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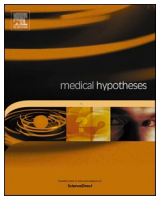

Hypothesis: Hypermobile Ehlers Danlos Syndrome is a determinant of fetal and young infant bone strength

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ABSTRACT

Several studies have demonstrated that young infants who present with unexplained fractures have a higher frequency of joint hypermobility, either in themselves or their parents, compared to the general population. The joint hypermobility is often associated with the autosomal dominant hypermobile form of Ehlers Danlos Syndrome (h-EDS) in which the mother is far more likely the affected parent. Most of these infants have metabolic bone disease as their radiographs often show poor bone mineralization. Some have alleged these infants were abused, while others have stated infants who have h-EDS or a parent with h-EDS are at increased risk to fracture as a result of a permanent, intrinsic connective tissue abnormality in the bone of the infant with h-EDS.

If these infants were not abused and the fractures were from an intrinsic bone abnormality with an increased risk to a fracture, this increased fracture risk would be expected to persist throughout the lifetime of the affected infant. However, this is not the case as the propensity to fracture in these infants is transient with few fractures after 6 months of age. This observation begs for another explanation for the etiology of the increased fracture risk as an infant, but much less so after 6 months of age.

I believe there is a different mechanism to explain this transient, increased fracture risk in infants with joint hypermobility from h-EDS born to mothers with h-EDS. In such a mother-infant pair with h-EDS the infant has joint hypermobility and the mother's uterus has hyperelasticity. I hypothesize that both of these factors cause diminished fetal bone loading when the infant with joint hypermobility strikes the uterus with hyperelasticity. Simple principles of physics are used to demonstrate this. Diminished fetal bone loading causes diminished fetal and young infant bone strength for the first 6 months of life that begins to normalize after about 6 months of age.

This hypothesis would explain the transient nature of the increased fracture risk for once born, these factors would cease to be present in the postnatal time period, but their influence would last for about 6 months. This finding has important implications in child abuse investigations of infants with unexplained fractures.

Background

a. Utah Paradigm and Fetal Bone Strength.

The Utah Paradigm is the contemporary model of bone physiology that can be used to understand factors that can promote bone strength and weakness [1]. This model recognizes the importance of the essential nutrients that produce bone including calcium, phosphate, vitamin D, and protein, but the centerpiece of the Utah Paradigm is the concept that bone loading is the critical determinant of bone strength. The Utah Paradigm postulates a regulatory system within bone that produces a bone strength that is appropriate for the load placed on the bone. This is done through a coordination of activities between the 3 types of bone cells: osteocytes, osteoblasts, and osteoclasts. Osteocytes are the mechanosensory cells that detect the load the bone experiences and are the mechanostat of the bone. The osteocyte is able to signal the effector cells, the osteoblasts and osteoclasts, to change bone strength if there is some change in the load the bone experiences. These changes in bone strength can occur by changes in bone density, bone architecture, or bone quality.

The Utah Paradigm also applies to the fetus as this system for regulating bone strength is established and fully functional during the second and third trimesters of pregnancy [1,2]. Using the Utah Paradigm to analyze risk factors in young infants with unexplained fractures, important determinants of both fetal and young infant bone strength have been appreciated over the past 25 years [3,4].

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Table 1
Studies that demonstrate fetal bone loading is an important determinant of fetal/young infant bone strength*.

First author [reference]	Subjects	Methodology Used	Conclusion
Rodriguez-a [6]	11 Newborns with CNMD	Radiographic and histology analysis	Reduction of intrauterine movement causes bone fragility
Rodriguez-b [7]	11 Newborns with CNMD	Quantitative bone parameters related to bone strength	Fetal immobilization produces fetal osteoporosis
Rodriguez-c [8]	Fetal akinesia	Histological study of curare induced immobilization in fetal rat bones	Fetal immobilization in utero produces fetal osteoporosis
Miller [2]	Premature infants	Theoretical comparison of bone loading in premature versus term infant	Prematurity is associated with decreased bone loading; Intrauterine environment is more favorable than the extrauterine environment in promoting bone strength
Miller [3]	Infants with TBBD	CT bone density compared to controls	Infants with TBBD had lower CT bone density compared to controls
Varghese [9]	Infants with TBBD	Bone architecture of radius determined and compared to controls	Infants with TBBD had less favorable bone architecture for bone strength compared to controls
Chan [10]	Newborns – SUC	DEXA; compared to controls with normal length	Newborns with SUC have lower bone mass
Tshorny [11]	Newborns – breech	TBUV compared to controls	Newborns born in breech have decreased TBUV
Ireland [12]	Newborns –breech	DEXA; compared to control vertex	Newborns born in breech have decreased bone density
Gursoy [13]	Newborns – twins	TBUV; compared to control singletons	Newborn twins have lower TBUV
Littner [14]	Newborns –LGA	TBUV; compared to control AGA	Newborns who are LGA have lower TBUV
Litmanovitz [15]	Premature infants who receive PT	TBUV; compared to controls – no PT	Minimal PT (bone loading) increases TBUV

* Abbreviations
CNMD = Congenital Neuromuscular Disorders
CT = Computed Tomography
TBBD = Temporary Brittle Bone Disease
DEXA = Dual Energy X-ray Absorptiometry
SUC = Short Umbilical Cord
TBUV = Tibial Bone Ultrasound Velocity
LGA = Large for Gestational Age
AGA = Appropriate for Gestational Age
PT = Physical Therapy.

The bone strength of the fetus and that of the infant in the first several months of postnatal life is, in part, determined by fetal bone loading through fetal movement [3]. Other factors that can also influence fetal/young infant bone strength are maternal provision of essential bone nutrients (calcium, phosphate, vitamin D, and protein to the fetus), prenatal exposure to drugs that can unfavorably influence bone strength, gestational diabetes, and gestational age [4]. When there is a deficiency of fetal bone loading or essential nutrients for bone formation, fetal bone weakness can result, and this condition has been called Metabolic Bone Disease of Infancy (MBDI) [4]. At an earlier time period in the 1990 and early 2000s when the determinants of fetal bone strength were less well-understood, this entity of transient infantile bone weakness was called Temporary Brittle Bone Disease (TBBD) [3,5]. Bone loading through fetal movement is likely the most important determinant of fetal/young infant bone strength, and multiple studies using various techniques and approaches have confirmed this as listed in Table 1 [2,3,6–15].

b. Fetal Movement.

Most primigravida mothers first appreciate fetal movement at 18 to 20 weeks, and most multipara mothers at 16 to 18 weeks. Fetal movements include whole-body movements, trunk movements, limb movements, breathing movements, hiccups, and stretching [16]. The healthy fetus has between 4 and 100 movements/hour with an average of about 40 movements/hour [17]. Thus, the estimated total number of fetal movements between 20 and 40 weeks in a normal term pregnancy is the (number of days) × (number of hours/day) × (number of movements/hour) = 140 × 24 × 40 = 134,400 fetal movements. It is estimated a mother appreciates only 40% of fetal movements, so this number may underestimate the true number of fetal movements [18].

In a normal pregnancy the fetus is moving in a pool of amniotic fluid in which the amniotic fluid volume relative to fetal volume is much greater in the early part of the second trimester and progressively decreases as the pregnancy approaches term gestation. Thus, fetal crowding occurs in the latter weeks of a normal pregnancy.

c. How Fetal Movement Affects Fetal Bone Strength.

The elegance of bone is its integrated composition of both a brittle material (mineral) and an elastic one (type 1 collagen). This composite make-up affords bones, especially long bones, the ability to bend when even the slightest force is applied to them.

The osteocyte is the “brain” of the regulatory system that controls bone strength to keep it in line with the load placed on the bone [1]. The osteocyte is buried in lacunae within bone and has multiple, thin cellular projections bathed in fluid that can detect even the slightest change in strain. Strain is the proportional change in length (change in length/length) caused by a load that can be from compression, tension, or shearing loads.

A force that is applied to the fetal skeleton generates a strain which registers within the osteocyte. Strain is the proportional change in length (change in length/length) caused by a load and can be from compression, tension, or shearing loads. If a bone is stretched by 1% of its length, then it is undergoing a strain of 1%, or 10,000 microstrain. If a bone is compressed by 0.1% of its original length so that it is now 99.9% of its original length, then it is undergoing a strain of 1000 microstrain. Loads will cause strains even when the loads are small.

This regulatory system that determines bone strength is functional during the fetal time period. Human fetal bone histology specimens

Table 2
Studies describing an association between joint hypermobility and infant bone fragility.

Study [reference]	Subjects	Findings
1. Paterson [5]	39 infants with TBBD	66% of parents had joint laxity
2. Miller [25]	60 infants with TBBD	6 infants (10%) had EDS
3. Paterson [26]	81 infants with TBBD	40 infants (49%) had at least one parent with Beighton score >4
4. Holick [27]	72 infants with MUF	67 infants (93%) had evidence of h-EDS
5. Miller [4]	75 infants with MBDI	15 cases (20%) with JH/h-EDS in either parent or infant

TBBD = Temporary Brittle Bone Disease.
MUF = Multiple Unexplained Fractures.
MBDI = Metabolic Bone Disease of Infancy.
JH = Joint Hypermobility.
EDS = Ehlers Danlos Syndrome.
h-EDS = hypermobile form of Ehlers Danlos Syndrome.

taken as early as 20 weeks gestational age show the presence of all 3 bone cell types (osteocytes, osteoblasts, and osteoclasts) [19]. Moreover, the Rodriguez studies and experimental studies using knockout mice with absent muscle show that this system is functional during the fetal time period in mice, rats, and humans [6–8,20].

There are likely 3 sources of forces during the fetal time period that can produce strains on bone and thus osteocyte activation to promote maintaining or increasing bone strength:

1. The main source of fetal bone loading is from the force on the fetal skeleton that occurs when the fetus hits the uterine wall from fetal movement. Extremity strikes against the wall of the uterus are likely the most efficient fetal movement to promote fetal bone strength. Of the greater than 100,000 fetal movements during a term pregnancy, extremity strikes of the arms and legs vary depending on the gestational age of the fetus. Hayat et al. showed that in the second trimester when the amniotic fluid volume is 70% of the intrauterine volume, the median frequency of arm movements was 35% and leg movements was 38%. Toward the end of the pregnancy when the fetal volume is 70% of the intrauterine volume, the median frequency of arm movements was 20% and leg movements was 15% [21]. The relative decrease in extremity strikes as the pregnancy moves toward term is likely a result of the relative intrauterine confinement from an increasing fetal volume and stable amniotic fluid volume.
2. Muscle contractions can also produce strains on the bones that the muscle is attached to. Because muscle strength will also increase with fetal movements and strikes against the uterine wall, muscle strength and bone strength are intricately and positively correlated with each other [20].
3. Like swimming, a fetus moving in amniotic fluid for some 20 weeks may also experience a drag force which could also theoretically cause bone strains and osteocyte activation [22].

The bone strength of the fetus at the time of delivery will, in great part, determine young infant bone strength and the risk for fragility fractures of the young infant in the first 6 months of life. Situations that decease fetal movement will decrease fetal bone strength, and include intrauterine confinement, fetal exposure to drugs that decrease movement, and fetal immobilization from congenital neuromuscular disorders. Noteworthy, factors that diminish bone strength have their greatest influence when the rate of bone growth is the greatest, and the fetal time period is the period of time of the highest rate of bone growth in the human [4].

Bone strength is determined by bone density, bone geometry, and bone quality. During the first six months of life, the diameter of a long bone such as the femur increases by about 50%, while the bone cortex thickness of the femur slightly decreases. The total bone mineral density of the femur, including both the cortical and trabecular bone density, decreases by about 30% with the cortical bone density decreasing by only 7% [23]. With these bone density and bone geometry changes, bone strength at 6 months of age is 3× greater than that at birth, thus emphasizing the critical influence of bone geometry on bone strength [24].

Hypotheses

1. Effect of Joint Hypermobility on Fetal Bone Loading.

A common risk factor that has been appreciated in infants with unexplained fractures in the first 6 months of life (infants with TBBD or MBDI) is joint hypermobility in either the parents and/or the infant. The joint hypermobility can be isolated, but is most often associated with the hypermobile type of Ehlers Danlos Syndrome (h-EDS).

Table 2 summarizes 5 studies that describe the association between joint hypermobility and fragility fractures in young infants [4,5,25–27]. Paterson and Miller have independently described an increased frequency of joint hypermobility in the child abuse-mimic Temporary Brittle Bone Disease (TBBD), and Holick reported h-EDS was prevalent in contested cases of child abuse. In both TBBD and MBDI the fracture susceptibility is in the first 6 months of life, suggesting the risk factors for these two conditions were primarily fetal in origin. It appears that the h-EDS risk factor also only influences bone strength in the first 6 months of life, an observation which is, in part, the basis of the two hypotheses below.

h-EDS is a systemic connective tissue disorder that is inherited in an autosomal dominant fashion. However, the idea that h-EDS is a distinct, single gene disorder has never been shown, and, at best, one can say h-EDS is multifactorial in origin with individuals having a 50% risk for inheriting all or some of the features of h-EDS from an affected parent [28]. When h-EDS is familial, mothers are far more likely to be the transmitting parent than fathers with some studies showing up to 90% of affected individuals with h-EDS being female [28].

Some have contended that the association between infants with MUF and h-EDS is based on abnormal bone quality or low bone density leading to an intrinsic postnatal bone weakness, especially when vitamin D deficiency is also present as a risk factor for bone weakness [27]. Studies of individuals with h-EDS have shown modestly lower bone density and modestly increased risk for fractures in older children and adults, but no dramatically increased risk for long bone and rib fractures in infants like there is in osteogenesis imperfecta [29]. However, the increased risk for fractures in young infants with h-EDS appears real, and like the other risk factors for MBDI, appears to be transient and not significantly affecting bone strength after 6 months of life. Infants with MBDI would have an average of 10 fractures at an average age of 9 weeks and then none after 6 months of life [4]. This suggests the risk factor of joint hypermobility, like bone loading from fetal movement, may have its effect during the fetal time period.

Others have suggested that there is no increased risk for bone fragility in young infants with unexplained fractures in which child abuse is alleged and in which the infant and/or parents have joint hypermobility or h-EDS [30].

Hypothesis 1. I hypothesize that fetal joint hypermobility affects fetal bone loading. Herein I present a qualitative analysis of the force that is generated from fetal bone loading on the skeleton in the fetus with normal joint laxity compared to that of the fetus with joint hypermobility.

2. Effect of uterine hyperelasticity on fetal bone loading

The uterus has 3 layers – the endometrium, myometrium, and perimetrium. The myometrium is the middle layer and contains muscle,

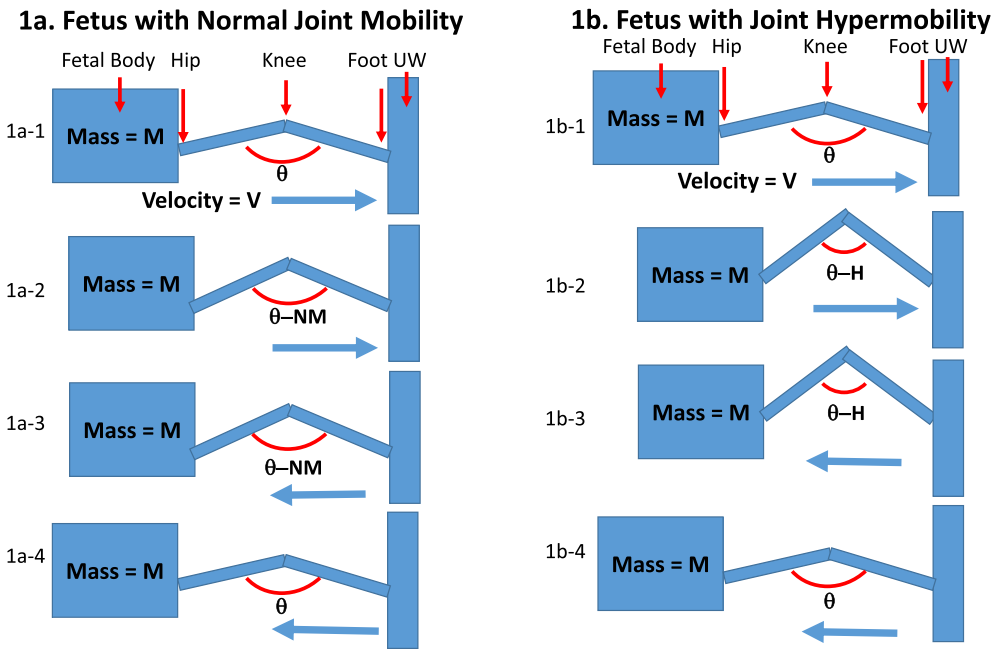

Fig. 1. Leg Strike of Fetus with Normal Joint Mobility (NM) Against Uterine Wall Compared to Fetus with Joint Hypermobility (H)
Definitions:

M = Mass of Fetus; V = Velocity of Fetus When Hits the Uterine wall; UW = Uterine Wall; θ = Initial Angle of Flexion of Knee, same for NM and H; θ-NM = Angle of Flexion of NM Knee After Strike; θ-H = Angle of Flexion of H Knee After Strike

Fig. 1a. Fetus with Normal Joint Mobility
Fig. 1a-1. The leg of a fetus with normal joint mobility is shown just before the leg hits the maternal uterine wall. The fetal body is represented by the large rectangle, the 3 joints of the leg (hip, knee, and ankle) are shown by red arrows, and the maternal uterine wall is shown by the narrow rectangle. The hip, knee, and foot all have angles of flexion while at rest. Only the flexion angle of rest for the knee is shown, angle θ.
Fig. 1a-2. When the fetus hits the maternal wall with velocity = V, the force of hitting the uterine wall causes all 3 leg joints to incur slight additional flexion. This is only shown for the knee which now is at an angle of θ-NM, just slightly less than θ. The hip and ankle would also experience slight additional flexion, but this is not shown in the figure.
Because the ankle, knee, and hip joints are of normal strength and mobility, there is minimal additional flexion of these joints, and the fetus immediately rebounds from the uterine wall with a relatively short time required for deceleration and with the leg in almost the same position as when it hit the uterine wall. The total time spent in contact with the uterine wall is the Deceleration Time = DT.
Fig. 1a-3. The fetus is now about to fully recoil from hitting the maternal uterine wall with the knee still at angle θ-NM.
Fig. 1a-4. The fetus is now fully recoiled and heading in the opposite direction with the knee now back to the resting flexion angle of θ.
Fig. 1b. Fetus with Joint Hypermobility
Fig. 1b-1. The leg of a fetus with joint hypermobility is shown just before the leg hits the maternal uterine wall. Except for the joint hypermobility, all factors are initially identical to those in Figure 1a with the fetus having the same mass = M and the leg hitting the maternal uterine wall with the same velocity = V and the same at-rest angles of flexion for all 3 leg joints.
Fig. 1b-2. When the fetus with joint hypermobility hits the maternal wall, the force of hitting the uterine wall causes all 3 leg joints to incur greater flexion of all 3 leg joints compared to the fetus with normal joint mobility. The greater the flexion of the knee, the smaller than angle on impact with the uterine wall. For the knee joint the flexion is θ-H, such that **θ-H < θ-NM.**
Most importantly, the time that the foot spends against the maternal uterine wall in the fetus with joint hypermobility will be greater than that in the fetus with normal joint mobility. Thus, the deceleration time in the fetus with joint hypermobility, DT-H, is greater than that in the fetus with normal joint mobility **DT-H > DTNM.**
Fig. 1b-3. The fetus is now about to fully recoil from hitting the maternal uterine wall with the knee still at angle θ-H.
Fig. 1b-4. The fetus is now fully recoiled and heading in the opposite direction with the knee now back to the resting flexion angle of θ.
The Figures show the 3 leg joints, but only shows the flexion angle for the knee. The hip and ankle would show similar changes in flexion angle as the for the knee. Moreover, the same process and thinking applies to the 3 joints of the arm (shoulder, elbow, and wrist). The fetus with joint hypermobility will have a greater deceleration time for all 3 arm joints when the arm hits the uterine wall compared to the fetus with normal joint mobility.
The significance of **DT-H > DT-NM** is that it indicates the force that a fetal skeleton realizes when it strikes the uterine wall is greater in the fetus with normal joint mobility compared to that of the fetus with joint hypermobility, as indicated from the following analysis:

F = Force on fetal skeleton upon hitting maternal uterine wall; M = Mass of fetus; V = Velocity of strike of fetus against maternal uterine wall; DT = Deceleration time; F = (M) (A) = (M) (V)/(DT)

F (normal joint mobility fetus) = (M) (V)/DT-NM; F (joint hypermobility fetus) = (M) (V)/DT-H
M and V are the same for both the fetus with normal joint mobility and the fetus with joint hypermobility.
DT-H > DT-NM; therefore
F (NM fetus) > F (H fetus)
Bone loading (NM fetus) > Bone loading (H fetus)

collagen and elastic fibers. The myometrium undergoes great change during the pregnancy to accommodate the growing fetus with the collagen content increasing 7 fold and the elastin content increasing 4–5 fold during pregnancy [31].

Most instances of joint hypermobility in infants with unexplained fractures involve h-EDS with the mother most often being the affected parent. h-EDS is a systemic disorder. Like the skin which is softer than normal in h-EDS and tendons and ligaments which are more hyperelastic in h-EDS than normal, it is likely the uterus in h-EDS is softer and more hyperelastic than the normal uterus. The following observations support this idea:

a. Scanning electron microscopy has demonstrated that the uterine wall contains elastic fibers in two forms: fibrils and thin sheets of elastic membranes arranged in a honeycomb fashion. It is thought that the elastin allows for normal expansion of the uterus during pregnancy so that the feus can occupy unencumbered intrauterine space. The elastin fibers are present in a spongelike matrix that contains flat sheets, or lamellae [32].
b. Transmission electron microscopy of the skin of patients with h-EDS show abnormalities in both collagen fibers and elastin fibers [33,34]
c. Transcriptome studies and cell culture studies indicate the pathogenesis of h-EDS is likely a result of abnormalities in connective tissue, most likely elastin and/or collagen and the interaction of these structural proteins with the extracellular matrix [35].

Hypothesis 2. I hypothesize that the composition and elasticity of the uterine wall also affects fetal bone loading. Herein I present a qualitative analysis of the force that is generated from fetal bone loading on the skeleton in the uterus with normal elasticity compared to that of the fetus with softness and hyperelasticity.

Theoretical considerations.

a. Joint Hypermobility versus Normal Joint Mobility

Using the basic physics equation F = MA, I calculated the relative force (F) that results from an extremity kick against the wall of the uterus in the fetus with normal joint mobility compared to that of the fetus with joint hypermobility as shown in Fig. 1a and b respectively in which.

M = the mass of the fetus.
A = the acceleration/deceleration when the fetus hits the uterine wall.
A = V/DT.
V = the velocity of the fetus hitting the wall of the uterus.
DT = the deceleration time, the time the fetal foot spends against the wall of the uterus before it recoils in the opposite direction.
F is thus is the load that the fetal skeleton would sense from a single extremity kick that would activate osteocytes that experienced a strain from this load.

b. Uterus with Hyperelasticity versus Uterus with Normal Elasticity

Using the same approach described above, I calculated the relative force (F) that results from an extremity kick of the fetus against the wall of a uterus with normal elasticity compared to the uterus of a mother with h-EDS in which the uterus has relative hyperelasticity and softness as shown in Fig. 2a and b.

c. Fetus with joint hypermobility in uterus with hyperelasticity as in h-EDS

Using the same approach described above, I calculated the relative force (F) that results from an extremity kick of the fetus with joint hypermobility against the wall of a uterus with hyperelasticity as shown in Fig. 3.

Predicted effect on the fetus.

a. Joint Hypermobility versus Normal Mobility.

Upon hitting the maternal uterine wall the analysis indicates that the extremity (arm or leg) of the fetus with joint hypermobility will have a greater deceleration time than the fetus with normal joint mobility. This arises because the joints of the extremity (arm = wrist, elbow, and shoulder; leg = foot, knee, and hip) in the fetus with joint hypermobility must all flex to a greater degree than the fetus normal joint mobility before the extremity fully rebounds from the uterine wall, thus requiring additional time for this additional flexion compared to the fetus with normal joint mobility.

A greater time for deceleration translates into a smaller force on the fetus, and thus a smaller force/load that is transmitted to the osteocytes of the skeletal system.

Force appreciated by osteocytes = F = M × V/Deceleration Time.
F (Normal joint mobility) > F (Joint Hypermobility).

Thus, on striking the uterine wall, fetal bone loading is less in a fetus with joint hypermobility compared to the fetus with normal joint mobility.

b. Uterus with Hyperelasticity versus Uterus with Normal Elasticity.

A uterus that is hyperelastic will dampen the force of a fetal extremity strike, and similar to fetal joint hypermobility, will increase the time for deceleration and thus decrease fetal bone loading.

Thus, on striking the uterine wall, fetal bone loading is less in the hyperelastic uterus of a woman with h-EDS compared to that of a woman with a uterus of normal elasticity.

c. Fetus with Joint Hypermobility in Uterus with Hyperelasticity as in h-EDS.

A pregnancy in which both the mother and fetus have h-EDS will have both of these factors that diminish fetal bone loading, and this situation will be the most extreme for causing bone fragility in the immediate postnatal period of time.

Discussion

The following conclusions can be drawn from our application of basic physics principles to how fetal joint hypermobility and uterine hyperelasticity affects fetal bone loading:

1. a fetus with joint hypermobility reared in a normal elasticity uterus experiences less fetal bone loading than a fetus with normal joint mobility reared in a normal elasticity uterus.
2. a fetus with normal joint mobility reared in a hyperelastic uterus experiences less fetal bone loading than a fetus with normal joint mobility reared in a normal elasticity uterus.
3. a fetus with joint hypermobility gestated in a hyperelastic uterus, such as occurs in a fetus and mother with-EDS, experiences significantly less fetal bone loading than described above in 1 and 2. The effects are likely additive.

These are not empirical results, but rather possible explanations for the published observations in Table 2 in which there has been a striking association between joint hypermobility and infant bone fragility.

If the hypothesis of diminished bone loading related to fetal

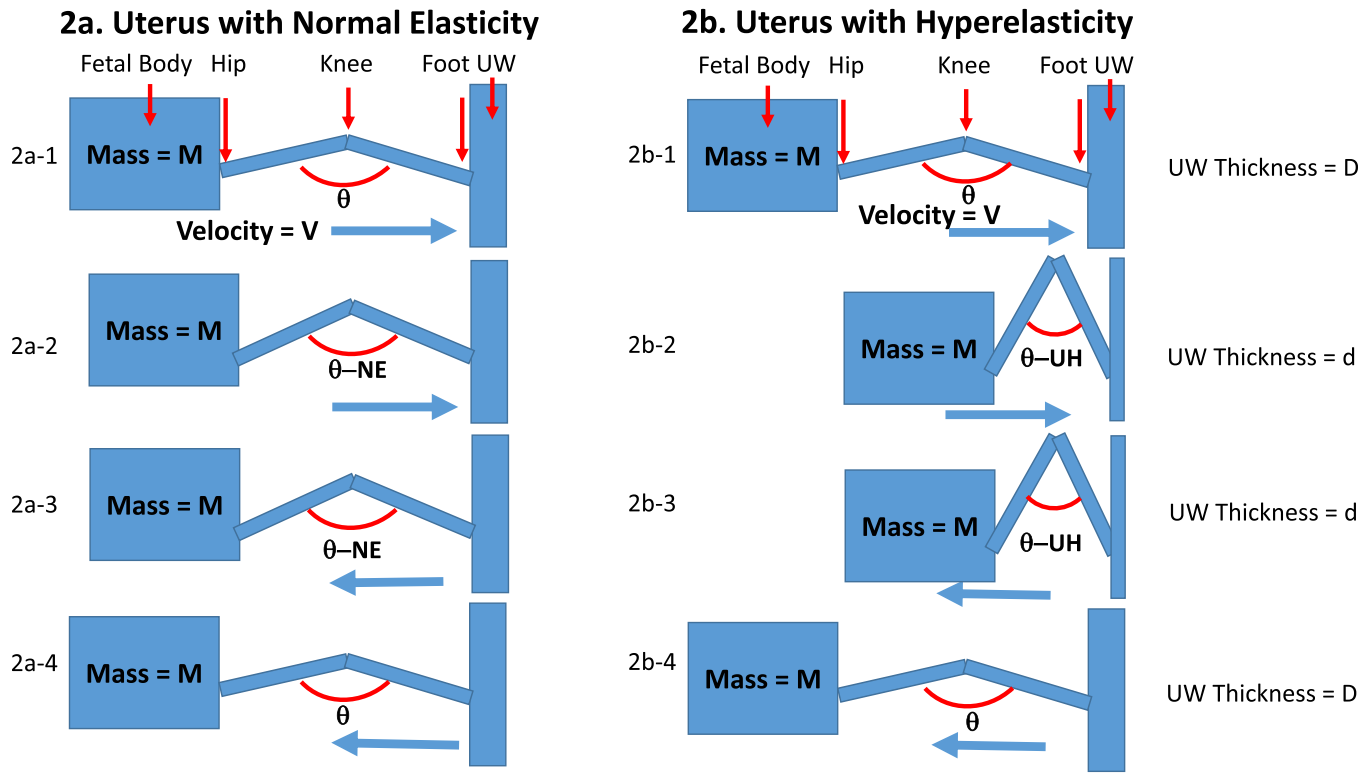

Fig. 2. Leg Strike of Fetus Against Uterine Wall of Normal Elasticity (NE) Compared to Uterus with Hyperelasticity (UH)

2a. Uterus with Normal Elasticity

Fig. 2a-1. The leg of the fetus with normal joint mobility hits a uterine wall of normal tissue elasticity (NE).

Fig. 2a-2. Because of the normal elasticity of the uterus there is no significant compression of the uterine tissue, so that the uterine wall remains essentially unchanged with a thickness of D. Moreover, the fetus has normal joint mobility so that the flexion of the 3 leg joints in hitting the uterus is minimal and the angle of flexion of the knee of θ-NE is just slightly less than θ.

Fig. 2a-3. The fetus then begins to recoil.

Fig. 2a-4. The fetus is fully recoiled and heading in the opposite direction.

2b. Uterus with Hyperelasticity

Fig. 2b-1. The leg of the fetus hits a uterine wall with tissue hyperelasticity in which the uterine wall thickness is initially D.

Fig. 2b-2. Because of the tissue hyperelasticity, there is compression of the uterine tissue so that the uterine wall thickness is now decreased to thickness d, a thickness that is less than the initial thickness of D.

Fig. 2b-3. The fetus then begins to recoil.

Fig. 2b-4. On fully recoiling the uterine compression is released, and the uterine wall thickness returns to D.

The time for this deceleration is DT-UH.

Noteworthy DT-UH > DT-NE

Like the fetal joint hypermobility analysis, the significance of **DT-UH > DT-NE** is the force that a fetal skeleton realizes when it strikes the uterine wall of normal elasticity is greater compared to that of the fetus who strikes a uterine wall of tissue hyperelasticity such as is seen in h-EDS.

F (normal uterine wall elasticity) = (M) (V)/ DT-NE

F (uterine wall hyperelasticity) = (M) (V)/ DT-UH

M and V are the same for both the fetus with normal joint mobility and the fetus with joint hypermobility.

DT-UH > DT-NE; therefore

F (NE) > F (UH)

Bone loading (NE) > Bone loading (UH)

hypermobility is correct, this would be a possible explanation for the observed association between infant and/or parental joint laxity (usually h-EDS with affected mother) and unexplained fractures in infants.

In the 5 studies noted in Table 2 the infant fractures are likely fragility fractures as there is almost always no bruising, no swelling, and no functional impairment unless they are long bone fractures. Moreover, in 2 of the series the authors note the frequency of infants with 4 or more rib fractures and no severe internal thoracic injury with respiratory distress – in Miller [3] it was 17/26 (65%), and in Miller [4] it was 36/75 (48%). This observation is further compelling evidence that these are fragility fractures as severe internal thoracic injury and respiratory distress would be expected in infants who had normal strength ribs [36].

Thus, fetal movement is the primary cause of developing normal bone strength in the newborn at the time of birth, and this can be analyzed from both a quantitative and qualitative perspective.

While the actual number of fetal movements is a quantitative determinant of fetal bone loading, the biomechanics of the interaction of fetal movement with the uterine wall is a qualitative determinant of fetal bone loading. Fetal joint laxity and uterine hyperelasticity can affect the load that a bone realizes when the fetus hits the uterine wall.

Hayat et al studied fetal movements at various gestational ages from 18 weeks gestation age to term using MRI and found the following [21]:

1. The frequency of all movement patterns including lower limb movements decreased with increasing gestational age.

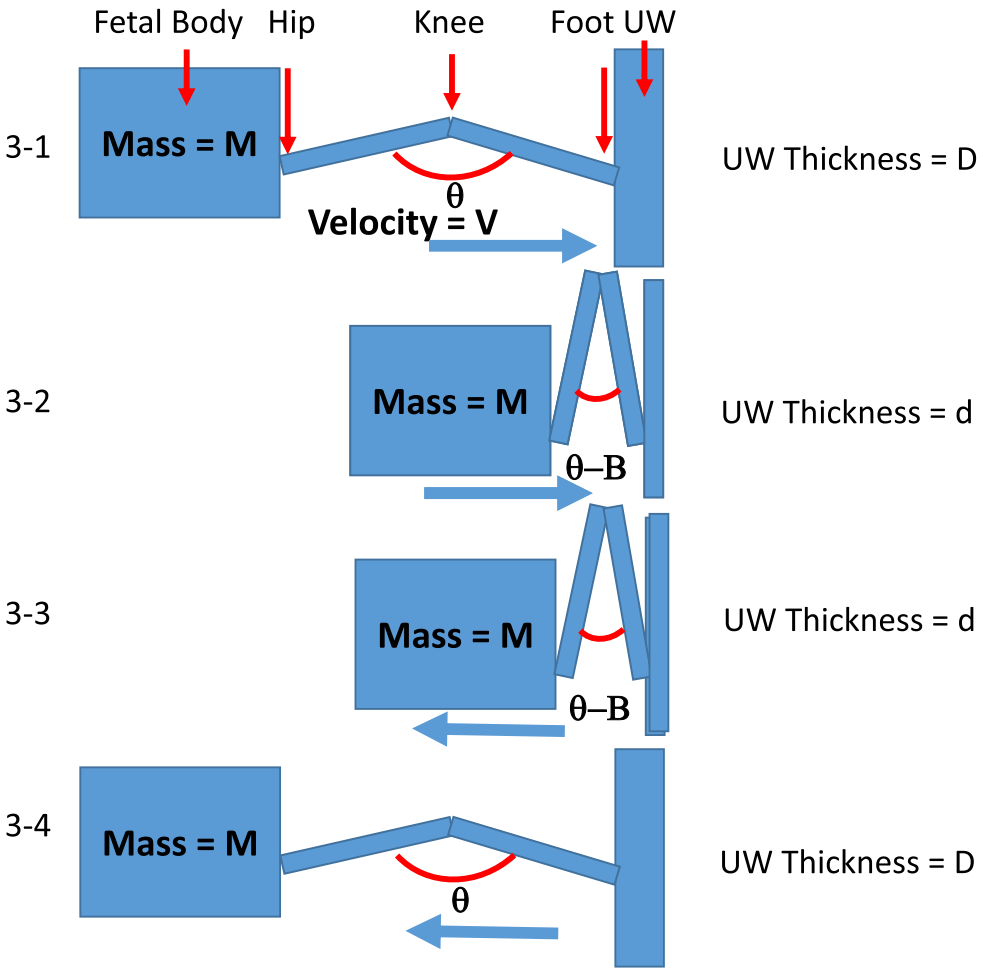

Fig. 3. Fetus with Joint Hypermobility Strikes Uterus with Hyperealsticity
Fig. 3-1. The leg of the fetus with joint hypermobility hits a uterine wall with tissue hyperelasticity in which the uterine all thickness is initially D.
Fig. 3-2. The additive effects of BOTH (B) the fetal joint hypermobility and uterine hyperelasticity cause the knee angle, θ-B, to be significantly less than either θ-H or θ-UH, and the uterine wall is compressed to d.
Fig. 3-3. The fetus then begins to recoil.
Fig. 3-4. On fully recoiling the uterine compression is released, the uterine wall thickness returns to D, and the knee joint angle returns to the pre-strike angle, θ. The time for this deceleration is DT-B.
Noteworthy DT-B > DT-H ≈ DT-HU > DT-N; Therefore
Bone loading (N) > Bone loading (H) ≈ Bone loading (UH) > Bone loading (B)
This combination of a fetus with joint hypermobility striking a uterine wall with hyperelasticity occurs in h-EDS.

2. There was a significant reduction in lower limb movement from 30 weeks gestational age to term that was associated with a high degree of flexion at the hip and knee joints
3. The fetal volume/total intrauterine volume doubled across this gestational range which likely explains the difference in the quantity and quality of movements.

   (Total intrauterine volume = fetal volume + amniotic fluid volume)

The different fetal movements will have different likelihoods of promoting fetal bone strength. Hiccups and stretching will have little effect on causing a strain that the osteocyte will appreciate. Trunk and whole body movements are appreciated as being strong movements by the mother and will likely cause local strains that may be transmitted more distally. These movements clearly can promote bone strength, but are likely no different in fetuses with normal joint mobility compared to those with joint hypermobility.

The fetal movements that are likely to be different in the hypermobile fetus compared to the normal mobility fetus in their ability to promote bone strength are the direct extremity hits of the fetus against the uterine wall. In the second trimester and early third trimester these extremity strikes are likely direct with no intrauterine confinement. However, in the latter part of the third trimester the extremity strikes occur in an environment of relative intrauterine confinement where the various joints of the extremities will be more flexed compared to earlier gestational ages as a result of the more limited space. This degree of flexion at different gestational ages will likely be less in the fetus with normal joint mobility compared to the fetus with hypermobility.

During a normal, full term pregnancy the tens of thousands of effective fetal movements that cause osetocyte activation are the critical quantitative determinant of fetal bone loading and strength. The interaction of fetal movement with the uterine wall is a qualitative determinant of fetal bone loading and strength. Not only is the quantity of fetal movement critical in determining fetal bone strength, but also the quality of the movement.

Table 3
Infant risk for bone fragility based on parental and infant phenotypes.

Mother Phenotype	Father Phenotype	Infant Phenotype	Infant Risk for Bone Fragility
Normal	Normal	Normal	Same as general population
Normal	h-EDS	Normal	Same as general population
Normal	Normal	JHM or h-EDS	1+ Increased because of fetal JHM
h-EDS	Normal	Normal	1+ Increased because of uterine environment
Normal	h-EDS	h-EDS	1+ Increased because of fetal JHM
h-EDS	Normal	h-EDS	2+ Increased because of uterine environment and fetal JHM
h-EDS	h-EDS	h-EDS	2+ Increased because of uterine environment and fetal JHM

Table 3 summarizes the relative risk of the various parental phenotypes and infant phenotypes for decreased fetal bone loading, and thus fetal/young infant bone strength.

Conclusion

Using the Utah Paradigm and basic physics principles this analysis indicates that the fetus with joint hypermobility, either isolated or related to h-EDS, produces less bone loading than the fetus with normal joint mobility. Moreover, if the mother also has h-EDS or some other connective tissue disorder that causes a hyperelastic uterine wall, the hyperelastic uterine wall might also be a less favorable environment for fetal bone loading. These observations could explain the increased risk for fragility fractures in infants with isolated joint hypermobility or in infants with joint hypermobility associated with h-EDS. Future studies on the possible causality between fetal and or maternal h-EDS and unexplained infant fractures are needed.

Consent statement/Ethical approval

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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